REMARKS

Claims 1-25, 52-58, and 62-86 are pending. With this reply, 87-89 are canceled without prejudice. Claims 1, 7, 13, 22, and 25 are amended with this reply. Claims 1 and 62 are independent. Support for the amendments can be found throughout the specification, for example, at paragraph 0099. No new matter has been added. Certain amendments to the claims are either in the nature of correcting typographical (e.g., claim 7) or grammatical errors (e.g., claims 13, 22 and 25) and therefore present no new issues. Applicants respectfully ask that the amendments be entered.

Claim Objections

The Examiner has objected to the phrase "to spiking target molecule" in claim 25, suggesting that the phrase is a typographical error. See the Office Action at page 2. Applicants have amended claim 25 to read "to spiking target molecules." It is believed this amendment obviates the objection.

Claim 7 was also objected to on the basis of a typographical error, which is corrected with this amendment.

Finally, the Examiner indicated that certain amendments to claims 13 and 22 failed to comply with 37 CFR 1.121. Applicants have corrected the amendments to those claims with this reply. Applicants believe the present reply complies with 37 CFR 1.121 in all respects.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 62-86 have been rejected under 35 U.S.C. § 112, second paragraph, indefiniteness.[1] The Examiner argues that independent claim 62 is unclear because "selectively cleavable bonds would no longer be present once contacted with a cleaving solution." See the Office Action at page 3. Applicants respectfully disagree.

[1] The Examiner indicated in the Advisory Action mailed October 25, 2007, that this rejection was withdrawn in view of the arguments presented in the reply filed October 5, 2007. Because Applicants' amendment was not entered, the arguments are presented again here. Applicants that the Examiner for indicating that Applicants' arguments were persuasive.

Applicants note that chemical reactions are not instantaneous. Although Applicants concede that while in contact with a cleaving solution, the selective cleavage reaction will proceed towards completion (i.e., selective cleavage of each and every selectively cleavable bond). However, at the first instant (and for some time after) the first and second probe molecules are in contact with a cleaving solution, fewer than all selectively cleavable bonds will be cleaved. In other words, during such time, there exists a (i.e., at least one) second probe molecule having at least one selectively cleavable bond. As such, the claim is not indefinite. Applicants respectfully request that the rejection under § 112, second paragraph, of claim 62 and the claims depending from it be reconsidered and withdrawn.

Rejection under 35 U.S.C. § 102(b)

Koster

Claims 1-16 and 87-89 have been rejected as being anticipated by U.S. Patent No. 6,043,031 to Koster et al. Claims 1 and 87 are independent. See the Office Action at pages 4-7. In particular, the Examiner argues with respect to claim 1 that Koster, e.g. at Figure 2, teaches that "[s]equence S and C are the instantly claimed first cleavage product . . . D2 is . . . the instantly claimed second cleavage product of the first probe molecule." See the Office Action at 4. Furthermore, "while Koster et al. do not specifically teach the ends of the molecules are the result of a cleavage reaction, these limitations are part of the process of making the probe array rather than structural limitations of the probe array." See the Office Action at 5. Although Applicants respectfully disagree that the phrase "cleavage product" is a process limitation rather than a structural limitation, the amendment to claim 1 overcomes the rejection over Koster without the need to address this contention in detail.

Claim 1 relates to a probe array for qualitative and/or quantitative detection of target molecules in a sample by molecular interactions between probe molecules and target molecules on the probe array. The probe array includes an array surface, a first cleavage product of a first probe molecule which includes a label, and a second cleavage product of the first probe molecule which is immobilized on the array surface. The first cleavage product is bound to a first region

of a target molecule, and the second cleavage product is bound to a second region of the target molecule. The array also includes a cleavage product of a second probe molecule immobilized on the array surface at a second defined site, wherein the cleavage product of the second probe molecule is not bound to a target molecule. The **cleavage products of the first and second probe molecules are in contact with a cleaving solution**. See independent claim 1.

Koster relates to DNA diagnostics based on mass spectrometry (see Title). In some embodiments Koster describes labels (e.g., M1, M2, and M3 in Figure 2) on detector oligonucleotides. See column 14, lines 14-30. Koster does not teach a probe array that includes **cleavage products of first and second probe molecules that are in contact with a cleaving solution**. Accordingly, Koster does not anticipate claim 1 and the claims that depend from it.

Claims 87-89 have been canceled. Applicants respectfully ask that the rejections over Koster be reconsidered and withdrawn.

Monforte

Claims 1-15, 62-76, 87 and 89 have been rejected as being anticipated by U.S. Patent No. 5,700,642 to Monforte et al. ("Monforte"). See the Office Action at 7-13. Claims 2-15 depend from claim 1; claims 63-76 depend from claim 62; and claim 89 depends from claim 87.

Claim 1 relates to a probe array including an array surface, a first cleavage product of a first probe molecule which includes a label, and a second cleavage product of the first probe molecule which is immobilized on the array surface. The first cleavage product is bound to a first region of a target molecule, and the second cleavage product is bound to a second region of the target molecule. The array also includes a cleavage product of a second probe molecule immobilized on the array surface at a second defined site, wherein the cleavage product of the second probe molecule is not bound to a target molecule. The **cleavage products of the first and second probe molecules are in contact with a cleaving solution**. See independent claim 1.

Claim 62 relates to a probe array including an array surface, a first probe molecule immobilized on the array surface having a label and a selectively cleavable bond between the site of immobilization on the array surface and the label, where the first probe molecule is bound to a

corresponding target molecule. A second probe molecule is also immobilized on the array surface, and has a label and a selectively cleavable bond between the site of immobilization on the array surface and the label. The second probe molecule is not bound to a corresponding target molecule. **The first and second probe molecules are in contact with a cleaving solution**. See independent claim 62.

The probe arrays of claim 1 and claim 62 each include probe molecules (or cleavage products of probe molecules) **bound to** target molecules and in contact with a cleaving solution.

Monforte describes modified oligonucleotide primers. The primers are immobilized and include cleavable bonds. The primers can be extended from their 3' ends and subsequently cleaved from an immobilized 5' end. See Abstract. However, Monforte does not teach a probe molecules (or cleavage products of probe molecules) **bound to** target molecules **and** in contact with a cleaving solution. Rather Monforte teaches that "amplified fragments **are denatured** . . . the amplified fragments containing the first primer are immobilized . . . and the non-immobilized amplified fragments are then removed, typically by washing. The first primer is then cleaved." (emphasis added) (col. 5, lines 40-47). The immobilized fragments are not bound to any other fragments at the time of cleavage. Similarly, at cols. 15-16, Monforte explains that after extension, "primer extension products **are denatured from the target**, typically using heat or a chemical denaturant such as formamide . . . primer extension products are then bound to the solid support . . . immobilized primer extension products . . . are then submitted to conditions effective to selectively cleave the cleavable site." (emphasis added). Again, in this description, the immobilized primer extension products are denatured from the target before cleavage.

Monforte therefore does not describe a probe array in which probe molecules (or cleavage products of probe molecules) are **bound to** target molecules **and** in contact with a cleaving solution at the same time.

Nor does Monforte teach an array having a cleavage product of a second probe molecule immobilized on the array surface at a second defined site, where **the cleavage product of the second probe molecule is not bound to a target molecule** (claim 1), or an array having a second probe molecule immobilized on the array surface having at least one label and at least

one selectively cleavable bond between the site of immobilization on the array surface and the label, where **the second probe molecule is not bound to a corresponding target molecule** (claim 62). Monforte's description of arrays is limited to column 24, line 57, to column 25, line 8, and does not include any description of array sites where a probe molecule **is not bound to a target molecule**. Rather, Monforte is directed to production of extended PCR products from each immobilized primer, which requires that **each immobilized primer** be bound to a target molecule (i.e., template nucleic acid). Therefore, Monforte teaches there are **no** array sites having single-stranded immobilized primers.

Since Monforte's description of arrays is limited to the cited passage (column 24, line 57, to column 25, line 8) and the two documents cited in Monforte's patent (Fodor and Southern), Monforte even fails to disclose arrays comprising probe molecules with cleavable bonds.

In view that

- Monforte on its own does not disclose method for preparation of arrays comprising probe molecules with cleavable bonds,

- neither Fodor nor Southern disclose arrays of probe molecules which could act as a primer and, in addition,

- the chemistries disclosed in Fodor and Southern cannot be used to synthesize Monforte's primers comprising cleavable bonds, Monforte's disclosure does not enable the person skilled in the art to prepare "an array of immobilized, cleavable primers."

Accordingly, Monforte does not teach all the limitations of claims 1 and 62, nor the claims that depend from them. Claims 87-89 have been canceled. Accordingly, Applicants respectfully ask that the Examiner reconsider and withdraw the rejection over Monforte under § 102(b).

Rejections under 35 U.S.C. § 103(a)

Fung

Claims 1, 15-16, 62, and 76-77 have been rejected as being obvious over Monforte in view of U.S. Patent No. 4,757,141 to Fung et al. ("Fung"). See the Office Action at page 14-18. Claims 15 and 16 depend from claim 1; claims 76-77 depend from claim 62.

As discussed above, Monforte fails to teach all the limitations of independent claims 1 and 62. In particular, Monforte does not teach a probe array in which probe molecules (or cleavage products of probe molecules) are **bound to** target molecules **and** in contact with a cleaving solution at the same time.. Fung does not remedy this defect.

Fung is directed generally to amino-derivatized phosphite and phosphate linking agents (see Fung at Title). Nothing in Fung teaches, suggests, or motivates a person having ordinary skill in the art to make a probe array in which probe molecules (or cleavage products of probe molecules) are **bound to** target molecules **and** in contact with a cleaving solution at the same time.

Applicants also respectfully disagree Fung teaches a detectable unit is coupled to probe molecules via an anchor group. The specification at page 40 describes that "the anchor groups are reacted with **specifically binding** components . . . which are detectable themselves or trigger a detectable reaction." The linking agents described in Fung do not engage in any specific binding. Rather, Fung teaches reagents that undergo covalent bond-forming reactions.

Because Monforte in view of Fung does not teach all of the limitations of claims 1, 15-16, 62, and 76-77 Applicants respectfully seek reconsideration and withdrawal of the rejection.

Lockhart

Claims 1, 17-18 and 22-25, 62, 78-79, and 83-86 have been rejected as being obvious over Monforte in view of U.S. Patent No. 6,040,138 to Lockhart et al. ("Lockhart"). See the Office Action at pages 18-26. Claims 17-18 and 22-25 depend from claim 1; claims 78-79 and 83-86 depend from claim 62.

As discussed above, Monforte fails to teach all the limitations of independent claim 1. In particular, Monforte does not teach a probe array in which probe molecules (or cleavage products of probe molecules) are **bound to** target molecules **and** in contact with a cleaving solution at the same time. See also independent claim 62. Lockhart does not remedy this defect.

Regarding claims 1 and 62, Lockhart teaches that only the non-immobilized member of a hybridized pair (i.e., the target) of nucleic acids carries a label. Lockhart does not describe any immobilized, labeled probes. See Lockhart, for example, at column 13, line 36 to column 14, line 36 (section titled "Labeling Nucleic Acids") describing, *inter alia*, that "'direct labels' . . . are directly attached to or incorporated into the target (sample) nucleic acid prior to hybridization. In contrast, 'indirect labels' are joined to the hybrid duplex after hybridization." Column 14, lines 16-20. In both cases, the label is never associated with an immobilized probe. The Examiner "agrees that **Lockhart does not teach the labeled probes are immobilized**; however, Lockhart is relied upon solely for the additional third, fourth, and fifth probes of the array." See the Office Action at "Response to Arguments," page 26 (emphasis added).

Independent claims 1 and 62 each relate to probe arrays in which probe molecules (or cleavage products of probe molecules) are **bound to** target molecules **and** in contact with a cleaving solution at the same time.. As described immediately above, **Lockhart does not teach the labeled probes are immobilized**, a point which the Examiner has conceded. Accordingly, the combination of teachings of Monforte and Lockhart fails to teach each and every element of independent claims 1 and 62. As such, there is no *prima facie* case of obviousness. Applicants therefore respectfully ask that the Examiner reconsider and withdraw the rejection of independent claims 1 and 62 and the claims that depend from them.

Mackay

Claims 1, 19, 62 and 80 have been rejected as being obvious over Monforte in view of U.S. Patent No. 5,700,642 to Mackay ("Mackay"). See the Office Action at pages 26-30. Claim 19 depends from claim 1 and claim 80 from claim 62.

As discussed above, Monforte fails to teach all the limitations of independent claims 1 and 62. In particular, Monforte does not teach a probe array having in which probe molecules (or cleavage products of probe molecules) are **bound to** target molecules **and** in contact with a cleaving solution at the same time. Mackay does not remedy this defect.

Mackay is directed to visualization of spots in an electrophoretic gel using a charge-coupled device (see Mackay at Abstract). Nothing in Mackay teaches, suggests, or motivates a person having ordinary skill in the art to make probe array having in which probe molecules (or cleavage products of probe molecules) are **bound to** target molecules **and** in contact with a cleaving solution at the same time.

In addition, Mackay does not teach a cleavage product of a probe molecule immobilized on an array surface at a defined site. Instead, Mackay relates to visualization of spots in an electrophoretic gel, a technique which requires that the molecules to be detected are mobile and not immobilized.

For at least the reasons given, Monforte in view of Mackay does not teach all the limitations of claims 1, 19, 62 and 80. Applicants respectfully ask that the rejection be reconsidered and withdrawn.

Lockhart and Kievits

Claims 20 and 81 has been rejected as being obvious over Monforte and Lockhart in view of U.S. Patent No. 5,770,360 to Kievits et al. ("Kievits"). See the Office Action at pages 30-32.

As discussed above, Monforte (alone, or in combination with Lockhart) fails to teach all the limitations of independent claims 1 and 62. In particular, Monforte does not teach a probe array in which probe molecules (or cleavage products of probe molecules) are **bound to** target molecules **and** in contact with a cleaving solution at the same time. Kievits does not remedy this defect.

Kievits is directed to elimination of false negatives in detection of amplified nucleic acids. Nothing in Kievtis teaches, suggests, or motivates a person having ordinary skill in the art

to make probe array in which probe molecules (or cleavage products of probe molecules) are **bound to** target molecules **and** in contact with a cleaving solution at the same time.

Applicants maintain their previous argument that Kievits does not teach the limitation for which it is cited. The Examiner argues that Kievits teaches probe molecules "which differ in their labeling degree (e.g., the probes are labeled differently [column 5, lines 32-37]; therefore the first probe is labeled to a high degree with a first label but not a second label, and vice versa for the second probe)." See the Office Action at page 11. Applicants respectfully disagree. The specification explains how probes differ in their degree of labeling "for example with a defined mixture of labeled and unlabelled probes varying in the form of a dilution series from array element to array element." In order to normalize a measurement, "the values of the detection standard elements . . . are plotted against the mixing ratio of labeled and unlabelled substance. This results in a calibration curve which indicates the dynamic range and the type of interdependence between the quantity of detectable units." (specification at 58-59).

The relevant portion of Kievits reads:

> In order to detect whether the analyte or the internal control is bound to the solid phase, two differently labeled detection probes now can be used. One will react specifically with the analyte bound to the solid phase . . . while **the second labeled detection probe, comprising a label that can be distinguished from the label on the first detection probe**, will react specifically with the internal control. The internal control used in this case must resemble the analyte in its capability of hybridizing to the immobilized oligonucleotide on the solid phase, but must differ from the analyte in that it will react with a different labeled detection probe than the analyte.

Kievits at column 5, lines 24-37 (emphasis added). **Kievits teaches a difference in kind—the labels can be distinguished from one another—not a difference in degree**. Claims 20 and 81 relate to probe arrays in which different array elements differ in their **labeling degree**, a feature not taught by Kievits, or by the combination of references.

For at least the reasons given, Monforte and Lockhart in view of Kievits do not teach all the limitations of claims 20 and 81. Applicants respectfully ask that the rejection be reconsidered and withdrawn.

Mackay and Kievits

Claims 21 and 82 have been rejected as being obvious over Monforte and Mackay in view of Kievits. See the Office Action at pages 32-33.

As discussed above, Monforte (alone, or in combination with Mackay) fails to teach all the limitations of independent claims 1 and 62. In particular, Monforte does not teach a probe array in which probe molecules (or cleavage products of probe molecules) are **bound to** target molecules **and** in contact with a cleaving solution at the same time. Kievits does not remedy this defect.

Kievits is directed to elimination of false negatives in detection of amplified nucleic acids. Nothing in Kievits teaches, suggests, or motivates a person having ordinary skill in the art to make probe array in which probe molecules (or cleavage products of probe molecules) are **bound to** target molecules **and** in contact with a cleaving solution at the same time.

Furthermore, as discussed above, Kievits does not teach detectable units arranged on different array elements which differ in their labelling degree.

For at least the reasons given, Monforte and Mackay in view of Kievits do not teach all the limitations of claims 21 and 82. Applicants respectfully ask that the rejection be reconsidered and withdrawn.

Stratagene Catalog

Claims 52-58 have been rejected as being obvious over Monforte in view of the 1998 Stratagene Catalog ("the catalog"). See the Office Action at pages 33-35. Claims 52-58 depend from claim 1.

As discussed above, Monforte fails to teach all the limitations of independent claim 1. In particular, Monforte does not teach a probe array in which probe molecules (or cleavage products of probe molecules) are **bound to** target molecules **and** in contact with a cleaving solution at the same time. The catalog does not remedy this defect.

The catalog describes various gene characterization kits, but nothing in the catalog teaches, suggests, or motivates a person having ordinary skill in the art to probe array in which probe molecules (or cleavage products of probe molecules) are **bound to** target molecules **and** in contact with a cleaving solution at the same time.

For at least this reason, Applicants believe claims 52-58 are patentable over Monforte in view of the catalog. Reconsideration and withdrawal of the rejection is respectfully sought.

CONCLUSION

Applicants ask that all claims be allowed. If the Examiner believes it to be helpful, the Examiner is invited to contact the undersigned representative by telephone at 202-429-3000. A petition for a three-month extension of time is enclosed with this reply. Please apply any charges or credits to deposit account 19-4293.

Respectfully submitted,

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